PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	22 DEC 2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PCT 21111Y	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/16336	23 May 2003 (23.05.2003)	29 May 2002 (29.05.2002)

Applicant

MERCK & CO., INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT 21111Y	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/16336	International filing date *(day/month/year)* 23 May 2003 (23.05.2003)	Priority date *(day/month/year)* 29 May 2002 (29.05.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/00, 35/00 and US Cl.: 424/114, 117; 514/183		
Applicant MERCK & CO., INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 June 2004 (25.06.2004)	15 December 2004 (15.12.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Dr. Kailash C. Srivastava Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/16336

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-33 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 34-67 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/16336

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-15	YES
	Claims NONE	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-15	NO
Industrial Applicability (IA)	Claims 1-15	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-15 lack an inventive step under PCT Article 33(3) as being obvious over Becker et al. (Inorganic and Medicinal Chemistry Letters, 2001, Volume 11, Pages 2719-1735) in view of Robinson et al. (U. S. Patent 5,863,949) and Clements et al. (Antimicrobial Agents and Chemotherapy, 2002,Volume 46, Number 6, Pages1793-1799). Becker et al. teach compounds having same basic structure as recited in Claims 1-6 and tables 1-2. Becker et al. also teach methods/ pathways (See Schemes 1-4) to prepare a variety of substituted compounds via substituting a variety of substituents to Position P1 of the structures 1 and 2 from an elaborate list of substituents that can be substituted at said position of the compounds having structure 1 and 2. Thus, a variety of therapeutic compounds or compounds having therapeutic value are produced. Note Becker et al. intrinsically teach preparation of compounds with a pharmaceutical carrier because they teach preparation of therapeutics. Becker et al., further teach enantiomers having structures of Tables 1 and 2 and substituents thereof substituted with said plurality of groups listed in Tables 1 and 2 and indicate that those compounds could be administered to alleviate a variety of matrix metalloprotein -mediated ailments (Abstract, Page 2719, Column 1, Lines 25-38 and Tables 1 and 2). Becker et al., however, do not teach inhibition of metabolic enzymes by administering said mixed with a matrix metalloprotein enzyme inhibitor compounds, or mixing an antibiotic with said compounds having structure claimed in Tables 1 and/or 2 to inhibit bacteria. Robinson et al. teach treatment of a variety of diseases, e.g., AIDS, sepsis, septic shock via administering compounds having the structure claimed in Clams 1-13 (Abstract) and Clements et al. teach inhibition of Escherichia coli with compounds having structures that Becker et al. teach and further demonstrate synergistic inhibition of Escherichia coli with said compounds and antibiotics, e.g., Ciproflaxicin (Table 2 and Figure 1). . Note that Clements et al. teach antibacterial activity of compounds that inhibit matrix metalloproteins, i.e., matrix metallo enzymes that constitute significant portion of bacterial genome (Page 1797, Column 2, Lines 9-13). Note that Clements et al teach same compounds having same structures and selection of same antibiotics as is instantly claimed to obtain same effect, i.e., an antibacterial activity. Thus, Clements et al. intrinsically teach combination of claimed compound with claimed selected antibiotics because the prior art method is teaching to select same compound with same structure and same antibiotic to obtain antibacterial activity via inhibiting the metalloprotein that is the same compound and antibiotic to obtain same effect as is claimed in the instant invention.

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Becker et al. with the beneficial teachings from Robinson et al. and Clements et al., because Robinson et al. teach methods to treat a variety of disease including sepsis and AIDS via administering compounds having the structure that Becker et al. teach, i.e., treatment of diseases/infections with inhibitors of matrix metallo proteins and Clements et al. teach antibacterial activity of matrix metallo proteins as well as the compounds having the same structure as those that Becker et al. teach. Thus, Robinson et al., remedy the deficiency in Becker et al's teachings of treating an infection via administering a compound of same structure that Becker at al. teach. Clements et al. remedy the deficiency in Becker et al's teachings of selecting an antibiotic in combination of same inhibitor of matrix metallo protein as is taught by Becker et al. to demonstrate antibacterial activity via inhibiting matrix metalloproteins in bacterial genome. The actual configuration of compounds or all the antibiotics claimed instantly are not the same as those taught in the cited prior arts. However, the adjustment of particular conventional working conditions (e.g., type and concentration of antibiotic employed in testing) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter that is well within the purview of the skilled artisan. In view of the fact that the applicant's invention also recites composition, method of making said composition and treating a disease via administering said compound, i.e., methods comprising the same steps and ingredients; applicant's invention is obvious over the teachings of Examiner-cited prior art references and therefore, does not have an inventive step.